Insulin-Like Growth Factor-I: a Key Regulator of Human Cancer Risk?

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In this issue of the Journal, Ma et al. *(1)* report the results of a nested case–control study that show an association between colorectal cancer risk in men and elevated plasma levels of insulin-like growth factor-I (IGF-I) and decreased plasma levels of IGF-binding protein-3 (IGFBP-3). Importantly, this study demonstrates these effects by using plasma samples drawn years before the clinical appearance of the tumor, thus minimizing the chance that plasma levels are influenced by the disease process. This study follows reports demonstrating associations between levels of IGF-I and/or IGFBP-3 and the risk for cancers of the breast, prostate, and lung, suggesting that IGF-I is an important indicator of risk for the most prevalent forms of cancer in Western society *(2–5).* In fact, IGF-I levels appear to have a stronger association than most other risk factors for these common cancers.

IGF-I is unique as a peptide growth factor. In addition to autocrine/paracrine functions demonstrated in numerous tissues, it serves as an endocrine hormone promoting postnatal somatic growth and maintaining lean tissue mass *(6).* IGF-I effects are modulated by a family of high-affinity BPs. IGF-I and its principal carrier protein, IGFBP-3, are produced primarily by the liver. Hepatic IGF-I synthesis is regulated by growth hormone (GH) and caloric intake and serves to integrate anabolic signals from the pituitary with signals related to nutritional status. In contrast to insulin, which is involved in short-term regulation of energy metabolism, changes in IGF-I levels occur over a longer term of days to weeks. Dietary restriction, which decreases the serum concentration of IGF-I in both humans and rodents, reduces the incidence of cancer in many rodent models *(7,8).* Caloric excess, on the other hand, may increase plasma IGF-I in humans *(9).* Perhaps part of the link between diet and cancer risk might be due to IGF-I and IGFBP-3.

Although Ma et al. find little evidence of an association between cancer risk and plasma measures of either total IGF-I or IGFBP-3 alone, they show by a number of different analyses

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that, when considered together, these two measures are important risk factors for colon cancer. One interpretation of these results is that unmeasured free IGF-I, which was not measured in the study, is the biologically relevant determinant. This is consistent with previous reports on breast, prostate, and lung cancers that found that inclusion of total IGF-I and IGFBP-3 together in multivariate analyses strengthened the associations with cancer risk. In circulation, more than 90% of IGF-I is bound by IGFBP-3 in a 150-kd complex that cannot cross the vascular endothelium, whereas free IGF-I can diffuse into tissue and exert biologic effects *(6)*. Interestingly, free IGFBP-3 can also cross into tissue and have biologic effects independent of IGF-I. In future studies, direct measurement of the concentration of free IGF-I and free IGFBP-3 in plasma might provide a more precise measure of cancer risk.

Regulation of serum IGF-I and IGFBP-3 levels includes genetic, environmental, and age-related factors. In population measurements, mean IGF-I and IGFBP-3 concentrations rise from birth to puberty and progressively decline throughout the remainder of life *(10)*. There is considerable variability within the population at each age, although intraindividual variability, particularly over a period of years, remains largely undescribed. It will be important to know within an individual how well measurement of IGF-I and IGFBP-3 at one time predicts levels at different ages and whether single measurements, or integrated measures of lifetime IGF-I and IGFBP-3 levels, are most useful for the estimation of cancer risk. A study of monozygotic and dizygotic twins suggested the concentration of IGF-I in serum is a heritable trait *(11)*. Genetic variability exists in both the IGF-I and IGFBP-3 genes *(12,13)*. Thus, polymorphic differences at these and other loci might contribute to interindividual variability and might also be useful predictors of risk.

A role for local regulation of IGF signaling on cancer cell biology is well documented. At the cellular level, IGF signaling is governed by the concentration of IGF-I and IGF-II, the number of IGF receptors on the cell surface, the mixture of BPs present, and the expression of specific BP proteases. In culture, IGF-I stimulates cell growth by increasing proliferation and by inhibiting apoptosis. Increased local production of IGF-I or IGF-II by tumors during the progression of breast, prostate, lung, colon, and other cancers is evidence that activation of the IGF type I receptor (IGF-IR) is important for neoplastic growth *in situ (14,15)*. In breast tumor tissue, IGF-IR protein is often overexpressed, possibly caused by loss of function of the p53 protein that binds to the IGF-IR promoter and represses transcription *(16–18)*. p53 also increases IGFBP-3 expression. Effects of IGFBP-3 include inhibition of cell proliferation and induction of apoptosis by preventing the interaction of IGF and IGF-IR and by an undescribed IGF-independent mechanism *(19,20)*. Finally, proteases such as prostate-specific antigen, which can cleave BPs and reduce their affinity for the ligands, may also contribute to neoplastic disease *(21)*.

Despite the extensive literature on how IGF signaling may contribute to cancer in a local context, the effects of plasma IGF-I and IGFBP-3 on this process are not well characterized. In a mouse experimental model of bladder cancer, reduction of serum IGF-I levels by dietary restriction slowed tumor progression coincident with decreased DNA synthesis and increased apoptosis in tumor cells *(22)*. All parameters were restored by infusion of recombinant IGF-I, showing that endocrine IGF-I is an important determinant of local activity and its effects on cell growth kinetics are key to its role in tumorigenesis. It will be important to determine, for colon cancer in particular, the activities of endocrine IGF-I within the existing well-described multistage model of carcinogenesis.

If IGF-I and IGFBP-3 are risk factors for common cancers, they could provide a strategy for cancer prevention. Diet is an interesting consideration in light of epidemiologic data and animal models that demonstrate an association with cancer risk. Controversy exists whether dietary fat and/or total caloric intake are risk factors for colon cancer; however, both may influence levels of IGF-I *(7,23)*. Chemoprevention strategies might include the use of agents, such as tamoxifen, fenretinide, or octreotide, all of which lower plasma IGF-I and are currently used in breast cancer prevention trials *(24–26)*. The efficacy of tamoxifen as a therapeutic and prophylactic agent is well documented. Although it is an estrogen receptor antagonist in mammary tissue, tamoxifen decreases disease recurrence in women with estrogen receptor-negative tumors; its effect on plasma IGF-I may contribute to its activity *(27)*. Fenretinide is a vitamin A derivative. In addition to lowering IGF-I, this compound increases circulating IGFBP-3, making it an attractive prevention candidate *(28)*. Finally, ocreotide belongs to the family of somatostatin analogs that suppress GH release from the pituitary and have antitumor activity in numerous cancer models.

Although the study by Ma et al. *(1)* provides perhaps the best epidemiologic evidence to date that plasma IGF-I and IGFBP-3 are associated with cancer risk, this result needs to be duplicated with other prospectively collected samples. Although plausible, it remains unknown whether IGF-I and IGFBP-3 are causal factors or simply surrogate measures of some other process. If IGF-I and IGFBP-3 are key regulators of human cancer risk, there are a number of important questions that remain. At what stage in the cancer process and in an individual's life are levels most critical? How do genetic, dietary, and environmental factors determine intraindividual and interindividual variation in IGF-I and IGFBP-3 levels? What is the relationship between IGF-I and IGFBP-3 that determines cancer risk? Can modulation of IGF-I and IGFBP-3 by preventive measures be used to reduce cancer risk without detrimental side effects? Of particular concern, therapeutic use of recombinant GH and IGF-I is being considered for numerous noncancer conditions including diabetes, renal failure, various catabolic syndromes, and age-associated tissue degeneration *(29–32)*. Would reduction of IGF-I levels for cancer prevention adversely affect these processes and would therapeutically increasing IGF-I affect cancer risk? In light of these issues, attempts to improve quality of life by modulating plasma IGF-I or IGFBP-3 must be approached with caution. Nevertheless, the studies by Ma et al. and others, suggesting that IGF-I and IGFBP-3 are major risk factors for neoplastic disease, promise new areas for studying the etiology, prevention, and therapy for the most common cancers in Western society.

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